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Dated 10 February 2003

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1.	Your reference	4-32740/NFI 8029
2.	Patent application number *(The Patent Office will fill in this part)*	0225679.0 — 4 NOV 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

		Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

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7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

9.	Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document	
	Continuation sheets of this form	
	Description	14
	Claim(s)	2
	Abstract	1
	Drawing(s)	
10.	If you are also filing any of the following, state how many against each item.	
	Priority documents	
	Translations of priority documents	
	Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
	Request for preliminary examination and search *(Patents Form 9/77)*	One
	Request for substantive examination *(Patents Form 10/77)*	
	Any other documents *(please specify)*	
11.		I/We request the grant of a patent on the basis of this application Signature: B.A. Yorke & Co B.A. Yorke & Co. Date: 04 November 2002
12.	Name and daytime telephone number of person to contact in the United Kingdom	Mrs. E. Cheetham 020 8560 5847

jm

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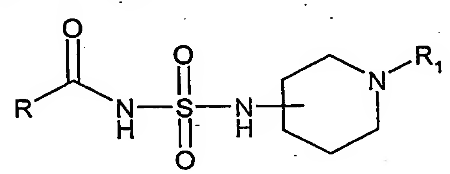
Organic Compounds

The present invention relates to organic compounds, e.g. useful in the treatment of disorders mediated by the action of steroid sulfatase.

In one aspect the present invention provides a phenylcarbonyl-sulfamic acid N-piperidinyl-amide, such as a compound of formula



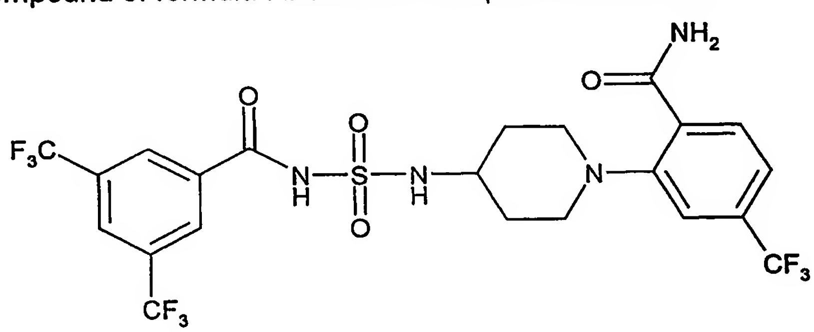
I

wherein

R is phenyl, e.g. unsubstituted phenyl or substituted phenyl, e.g. substituted by one or more groups as conventional in organic chemistry, e.g. substituted by one or more (C_{1-6})haloalkyl, such as CF_3, or halogen, and

R_1 is alkoxycarbonyl, e.g. (C_{1-6})alkoxycarbonyl, such as tert.butoxycarbonyl; or unsubstituted or substituted phenyl, e.g. substituted by one or more groups as conventional in organic chemistry, such as phenyl substituted by one or more (C_{1-6})haloalkyl, (C_{1-4})alkylcarbonyl, aminocarbonyl, halogen, (C_{1-6})haloalkyl.

A preferred compound of formula I includes a compound of formula



I_s

A compound of formula I includes a compound of formula I_S. Compounds provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". Each single substituent defined above in a compound of the present invention may be per se a preferred substituent, independently of the other substituents defined.

In a compound of the present invention the piperidine ring may be attached to the amine group in any position, e.g. in position 2, 3 or 4 and is preferably attached in position 4.

A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides a compound of the present invention in the form of a salt.

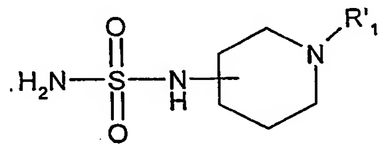
A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt, an acid addition salt or an amine salt. Metal salts include for example alkali or earth alkali salts; acid addition salts include salts of a compound of the present invention with an acid, e.g. HCl; amine salts include salts of a compound of the present invention with an amine.
A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.

A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomers or diastereoisomeres and mixtures thereof, e.g. racemates. A compound of the present invention may exist in the form of isomers and mixtures thereof. Isomeric, e.g. including enantiomeric or diasteromeric, mixtures may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. or as specified herein.

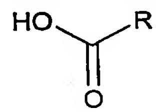
In another aspect the present invention provides a process for the production of a compound of the present invention comprising reacting

In another aspect the present invention provides a process for the production of a compound of the present invention comprising reacting an N-piperidine substituted sulfamic acid amide, wherein one amine group is unsubstituted, e.g. of formula



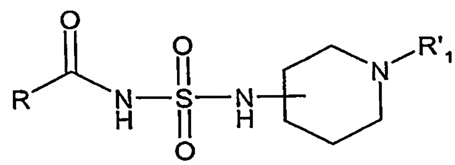
II

wherein R'_1 is as defined R_1 above and additionally may be hydrogen, with a phenylcarboxylic acid, e.g. a compound of formula



III

wherein R is as defined above, e.g. in an activated form, such as in the form of an carboxylic acid chloride, e.g. or in the presence of a coupling agent; and isolating a phenylcarbonyl-sulfamic acid N-piperidinyl-amide, e.g. a compound of formula

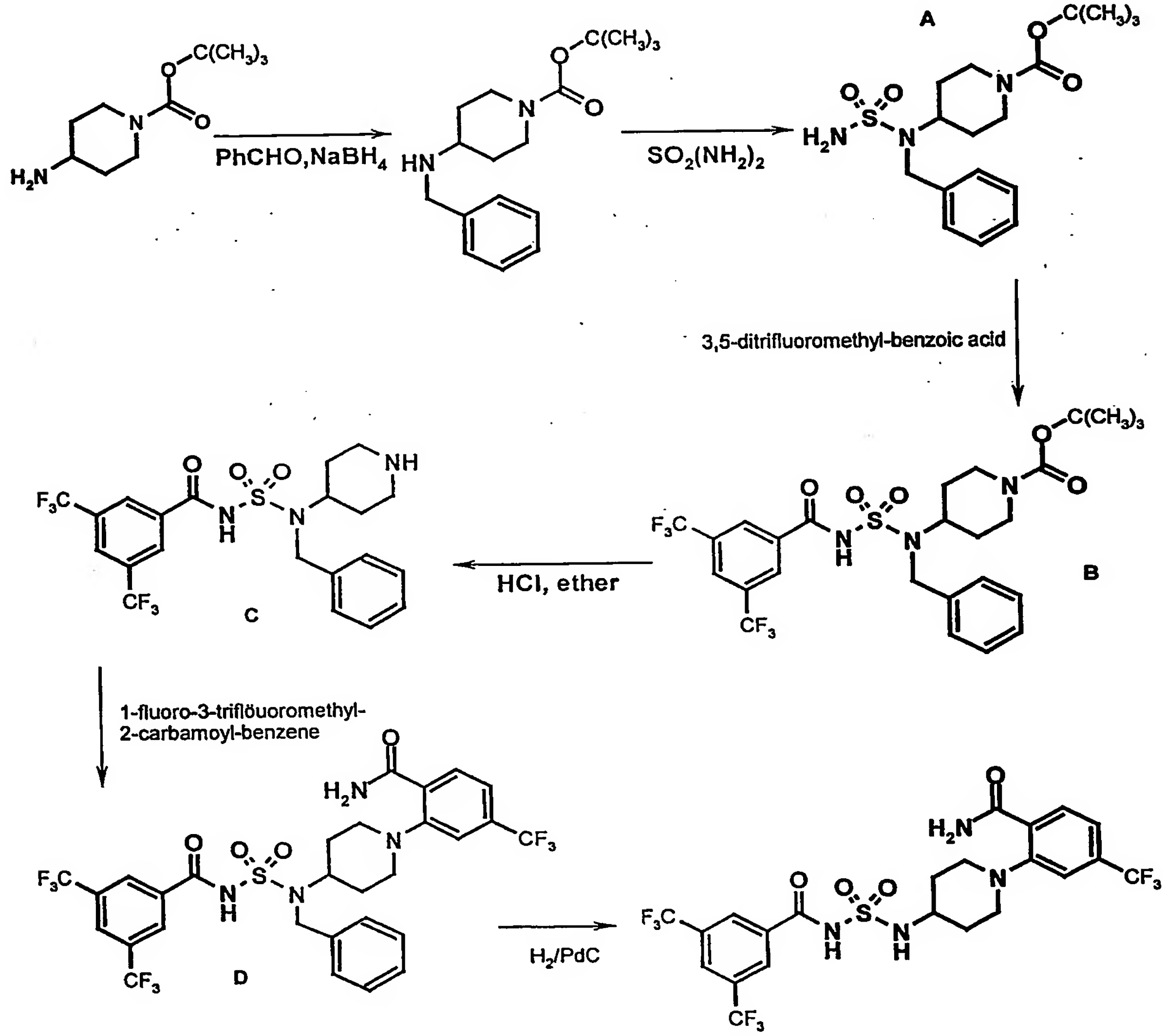


I'

obtained from the reaction mixture obtained, and, if R'_1 is hydrogen, further reacting a compound of formula I' to obtain a compound of formula I, wherein R and R_1 are as defined above, e.g. acylating a compound of formula I' with an acylation agent, to obtain a compound of formula I, wherein R_1 is alkoxycarbonyl.

The above reaction is an acylation reaction and may be carried out as appropriate, e.g. in appropriate solvent and at appropriate temperatures, e.g. according to a method as conventional or according to a method as described herein.
An N-piperidine substituted sulfamic acid amide, wherein one amine group is unsubstituted, such as a compound of formula II, may e.g. be obtained from carbamic acid, by reaction with a piperidinamine., e.g. in an activated form. Compounds of formula II and III are known or may be obtained as appropriate, e.g. according to a method as conventional or as described herein. Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional, e.g. or as described herein.

Alternatively a compound of the present invention may be prepared according to the following reaction scheme:



e.g. according to the method as set out in Example 1 below.

Steroidal hormones in particular tissues are associated with several diseases, such as tumors of breast, endometrium and prostate and disorders of the pilosebaceous unit, e.g. acne, androgenetic alopecia, and hirsutism. Important precursors for the local production of these steroid hormones are steroid 3-O-sulfates which are desulfated by the enzyme steroid sulfatase in the target tissues. Inhibition of this enzyme results in reduced local levels of the corresponding active steroidal hormones, which is expected to be of therapeutic relevance.

Furthermore, steroid sulfatase inhibitors may be useful as immunosuppressive agents, and have been shown to enhance memory when delivered to the brain.

Acne is a polyetiological disease caused by the interplay of numerous factors, such as inheritance, sebum, hormones, and bacteria. The most important causative factor in acne is sebum production; in almost all acne patients sebaceous glands are larger and more sebum is produced than in persons with healthy skin. The development of the sebaceous gland and the extent of sebum production is controlled hormonally by androgens; therefore, androgens play a crucial role in the pathogenesis of acne. In man, there are two major sources supplying androgens to target tissues: (i) the gonades which secrete testosterone, (ii) the adrenals producing dehydroepiandrosterone (DHEA) which is secreted as the sulfate conjugate (DHEAS). Testosterone and DHEAS are both converted to the most active androgen, dihydrotestosterone (DHT), in the target tissue, e.g. in the skin. There is evidence that these pathways of local synthesis of DHT in the skin are more important than direct supply with active androgens from the circulation. Therefore, reduction of endogeneous levels of androgens in the target tissue by specific inhibitors should be of therapeutic benefit in acne and seborrhoea. Furthermore, it opens the perspective to treat these disorders through modulation of local androgen levels by topical treatment, rather than influencing circulating hormone levels by systemic therapies.

Androgenetic male alopecia is very common in the white races, accounting for about 95% of all types of alopecia. Male-pattern baldness is caused by an increased number of hair follicles in the scalp entering the telogen phase and by the telogen phase lasting longer. It is a genetically determined hair loss effected through androgens. Elevated serum DHEA but normal testosterone levels have been reported in balding men compared with non-balding controls, implying that target tissue androgen production is important in androgenetic alopecia.

Hirsutism is the pathological thickening and strengthening of the hair which is characterized by a masculine pattern of hair growth in children and women. Hirsutism is androgen induced, either by increased formation of androgens or by increased sensitivity of the hair follicle to androgens. Therefore, a therapy resulting in reduction of endogeneous levels of androgens and/or estrogens in the target tissue (skin) should be effective in acne, androgenetic alopecia and hirsutism.

As described above, DHT, the most active androgen, is synthesized in the skin from the abundant systemic precursor DHEAS and the first step in the metabolic pathway from DHEAS to DHT is desulfatation of DHEAS by the enzyme steroid sulfatase to produce

DHEA. The presence of the enzyme in keratinocytes and in skin-derived fibroblasts has been described. The potential use of steroid sulfatase inhibitors for the reduction of endogenous levels of steroid hormones in the skin was confirmed using known steroid sulfatase inhibitors, such as estrone 3-O-sulfamate and 4-methylumbelliferyl-7-O-sulfamate. We have found that inhibitors of placental steroid sulfatase also inhibit steroid sulfatase prepared from either a human keratinocyte (HaCaT) or a human skin-derived fibroblast cell line (1BR3GN). Such inhibitors were also shown to block steroid sulfatase in intact monolayers of the HaCaT keratinocytes.

Therefore, inhibitors of steroid sulfatase may be used to reduce androgen and estrogen levels in the skin. They can be used as inhibitors of the enzyme steroid sulfatase for the local treatment of androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhoea, androgenetic alopecia, hirsutism) and for the local treatment of squamous cell carcinoma.

Furthermore non-steroidal steroid sulfatase inhibitors are expected to be useful for the treatment of disorders mediated by the action of steroid hormones in which the steroidal products of the sulfatase cleavage play a role. Indications for these new kind of inhibitors include androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhea, androgenetic alopecia, hirsutism); estrogen- or androgen-dependent tumors, such as squamous cell carcinoma and neoplasms, e.g. of the breast, endometrium, and prostate; inflammatory and autoimmune diseases, such as rheumatoid arthritis, type I and II diabetes, systemic lupus erythematosus, multiple sclerosis, myastenia gravis, thyroiditis, vasculitis, ulcerative colitis, and Crohn's disease, psoriasis, contact dermatitis, graft versus host disease, eczema, asthma and organ rejection following transplantation. Steroid sulfatase inhibitors are also useful for the treatment of cancer, especially for the treatment of estrogen- and androgen-dependent cancers, such as cancer of the breast and endometrium and squamous cell carcinoma, and cancer of the prostata. Steroid sulfatase inhibitors are also useful for the enhancement of cognitive function, especially in the treatment of senile dementia, including Alzheimer's disease, by increasing the DHEAS levels in the central nervous system.

Activities of compounds in inhibiting the activity of steroid sulfatase may be shown in the following test systems:

Purification of human steroid sulfatase

Human placenta is obtained freshly after delivery and stripped of membranes and connective tissues. For storage, the material is frozen at -70°C. After thawing, all further steps are carried out at 4°C, while pH values are adjusted at 20°C. 400 g of the tissue is homogenized in 1.2 l of buffer A (50 mM Tris-HCl, pH 7.4, 0.25 M sucrose). The homogenate obtained is centrifuged at 10,000xg for 45 minutes. The supernatant is set aside and the pellet obtained is re-homogenized in 500 ml of buffer A. After centrifugation, the two supernatants obtained are combined and subjected to ultracentrifugation (100,000xg, 1 hour). The pellet obtained is resuspended in buffer A and centrifugation is repeated. The pellet obtained is suspended in 50 ml of 50 mM Tris-HCl, pH 7.4 and stored at -20°C until further work-up.

After thawing, microsomes are collected by ultracentrifugation (as descrobed above) and are suspended in 50 ml of buffer B (10 mM Tris-HCl, pH 7.0, 1 mM EDTA, 2 mM 2-mercaptoethanol, 1 % Triton X-100, 0.1 % aprotinin). After 1 hour on ice with gentle agitation, the suspension is centrifuged (100,000xg, 1 hour). The supernatant containing the enzyme activity is collected and the pH is adjusted to 8.0 with 1 M Tris. The solution obtained is applied to a hydroxy apatite column (2.6x20 cm) and equilibrated with buffer B, pH 8.0. The column is washed with buffer B at a flow rate of 2 ml/min. The activity is recovered in the flow-through. The pool is adjusted to pH 7.4 and subjected to chromatography on a concanavalin A sepharose column (1.6x10 cm) equilibrated in buffer C (20 mM Tris-HCl, pH 7.4, 0.1 % Triton X-100, 0.5 M NaCl). The column is washed with buffer C, and the bound protein is eluted with 10 % methyl mannoside in buffer C. Active fractions are pooled and dialysed against buffer D (20 mM Tris-HCl, pH 8.0, 1 mM EDTA, 0.1 % Triton X-100, 10 % glycerol (v/v)).

The retentate obtained is applied to a blue sepharose column (0.8x10 cm) equilibrated with buffer D; which column is washed and elution is carried out with a linear gradient of buffer D to 2 M NaCl in buffer D. Active fractions are pooled, concentrated as required (Centricon 10), dialysed against buffer D and stored in aliquots at -20°C.

Assay of Human Steroid Sulfatase

It is known that purified human steroid sulfatase not only is capable to cleave steroid sulfates, but also readily cleaves aryl sulfates such as 4-methylumbelliferyl sulfate which is used in the present test system as an activity indicator. Assay mixtures are prepared by consecutively dispensing the following solutions into the wells of white microtiter plates:

1) 50 µl substrate solution (1.5 mM 4-methylumbelliferyl sulfate in 0.1 M Tris-HCl, pH 7.5)

2) 50 µl test compound dilution in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100 (stock solutions of the test compounds are prepared in DMSO; final concentrations of the solvent in the assay mixture not exceeding 1 %)
3) 50 µl enzyme dilution (approximately 12 enzyme units/ml)

We define one enzyme unit as the amount of steroid sulfatase that hydrolyses 1 nmol of 4-methylumbelliferyl sulfate per hour at an initial substrate concentration of 500 µM in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100, at 37°C.
Plates are incubated at 37°C for 1 hour. Then the reaction is stopped by addition of 100 µl 0.2 M NaOH. Fluorescence intensity is determined in a Titertek Fluoroskan II instrument with λ_{ex} = 355 nm and λ_{em} = 460 nm.

Calculation of relative IC_{50} values
From the fluorescence intensity data (I) obtained at different concentrations (c) of the test compound in the human steroid sulfatase assay as described above, the concentration inhibiting the enzymatic activity by 50 % (IC_{50}) is calculated using the equation:

$$I = \frac{I_{100}}{1 + (c / IC_{50})^s}$$

wherein I_{100} is the intensity observed in the absence of inhibitor and s is a slope factor. Estrone sulfamate is used as a reference compound and its IC_{50} value is determined in parallel to all other test compounds. Relative IC_{50} values are defined as follows:

$$\text{rel } IC_{50} = \frac{IC_{50} \text{ of test compound}}{IC_{50} \text{ of estrone sulfamate}}$$

According to our testing and calculation estrone sulfamate shows an IC_{50} value of approximately 60 nM.
The compounds of the present invention show activity in that described assay.

CHO/STS Assay
CHO cells stably transfected with human steroid sulfatase (CHO/STS) are seeded into microtiter plates. After reaching approximately 90% confluency, they are incubated overnight with graded concentrations of test substances (e.g. compounds of the present invention). They are then fixed with 4% paraformaldehyde for 10 minutes at room temperature and washed 4 times with PBS, before incubation with 100 µl/well 0.5 mM 4-methylumbelliferyl

sulfate (MUS), dissolved in 0.1M Tris-HCl, pH 7.5. The enzyme reaction is carried out at 37°Cfor 30 minutes. Then 50µl/well stop solution (1M Tris-HCl, pH 10.4) are added. The enzyme reaction solutions are transferred to white plates (Microfluor, Dynex, Chantilly, VA) and read in a Fluoroskan II fluorescence microtiter plate reader. Reagent blanks are subtracted from all values. For drug testing, the fluorescence units (FU) are divided by the optical density readings after staining cellular protein with sulforhodamine B (OD_{550}), in order to correct for variations in cell number. IC_{50} values are determined by linear interpolation between two bracketing points. In each assay with inhibitors, estrone 3-O-sulfamate is run as a reference compound, and the IC_{50} values are normalized to estrone 3-O-sulfamate (relative IC_{50} = IC_{50} compound / IC_{50} estrone 3-O-sulfamate).
The compounds of the present invention show activity in that described assay.

Assay Using Human Skin Homogenate
Frozen specimens of human cadaver skin (about 100 mg per sample) are minced into small pieces (about 1x1 mm) using sharp scissors. The pieces obtained are suspended in ten volumes (w/w) of buffer (20 mM Tris-HCl, pH 7.5), containing 0.1 % Triton X-100. Test compounds (e.g. compounds of the present invention) are added at graded concentrations from stock solutions in ethanol or DMSO. Second, DHEAS as the substrate is added (1 µC/ml [^{3}H]DHEAS, specific activity: about 60 Ci/mmol, and 20 µM unlabeled DHEAS). Samples are incubated for 18 hrs at 37°C. At the end of the incubation period, 50 µl of 1 M Tris, pH 10.4 and 3 ml of toluene are added. A 1-ml aliquot of the organic phase is removed and subjected to liquid scintillation counting. The determined dpm-values in the aliquots are converted to nmol of DHEA cleaved per g of skin per hour.
The compounds of the present invention show activity in that described assay.

The compounds of the present invention show activity in test systems as defined above. A compound of the present invention in salt and/or solvate form exhibits the same order of activity as a compound of the present invention in free and/or non-solvated form.
The compounds of the present invention are therefore indicated for use as steroid sulfatase inhibitors in the treatment of disorders mediated by the action of steroid sulfatase, e.g. including androgen-dependent disorders of the pilosebaceous unit, such as
- acne,
- seborrhea,
- androgenetic alopecia,

- -hirsutism;
- cancers, such as estrogen and androgen-dependent cancers;
- cognitive dysfunctions, such as senile dementia including Alzheimer's disease.

The compounds of the present invention are preferably used in the treatment of acne, seborrhea, androgenetic alopecia, hirsutism; estrogen, e.g. and androgen-dependent cancers, more preferably in the treatment of acne. Treatment includes therapeutical treatment and prophylaxis.

The use of a phenylcarbonyl-sulfamic acid N-piperidinyl-amide, e.g. a compound of the present invention, as steroid sulfatase inhibitors is novel.

In another aspect the present invention provides the use of a phenylcarbonyl-sulfamic acid N-piperidinyl-amide, e.g. a compound of the present invention, in the preparation of a medicament for the treatment of a disorder mediated by the action of steroid sulfatase, e.g. a disorder responsive to the inhibition of the action of steroid sulfatase, most preferably acne.

In another aspect the present invention provides a compound of formula I for use as a pharmaceutical, e.g. in the treatment of disorders mediated by the action of steroid sulfatase.

In a further aspect the present invention provides a compound of the present invention, e.g. a compound of formula I, for use in the preparation of a medicament for treatment of disorders mediated by the action of steroid sulfatase.

In another aspect the present invention provides a method of treating disorders mediated by the action of steroid sulfatase comprising administering a therapeutically effective amount of a sulfamic acid ester of the present invention, e.g. a compound of formula I, to a subject in need of such treatment.

For such use the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results may be obtained if the compounds are administered at a daily dose of from about 0.1 mg/kg to about 100 mg/kg animal body weight, e.g. conveniently administered in divided doses two to four times daily. For most large mammals the total daily

dosage is from about 5 mg to about 5000 mg, conveniently administered, for example, in divided doses up to four times a day or in retarded form. Unit dosage forms comprise, e.g. from about 1.25 mg to about 2000 mg of a compound of a present invention in admixture with at least one pharmaceutically acceptable excipient, e.g. carrier, diluent.
The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt, metal salt, amine salt; or in free form; optionally in the form of a solvate.
The compounds of the present invention may be administered in similar manner to known standards for use in such indications. The compounds of the present invention may be admixed with conventional, e.g. pharmaceutically acceptable, excipients, such as carriers and diluents and optionally further excipients. The compounds of the present invention may be administered, e.g. in the form of pharmaceutical compositions,
- orally, e.g. in the form of tablets, capsules;
- parenterally, intravenously, e.g. in the form of liquids, such as solutions, suspensions;
- topically, e.g. in the form of ointments, creams.

The concentrations of the active substance in a pharmaceutical composition will of course vary, e.g. depending on the compound used, the treatment desired and the nature of the composition used. In general, satisfactory results may be obtained at concentrations of from about 0.05 to about 5 % such as from about 0.1 to about 1% w/w in topical compositions, and by about 1% w/w to about 90% w/w in oral, parenteral or intravenous compositions.

In another aspect the present invention provides a pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of the present invention in association with at least one pharmaceutically acceptable excipient.

A pharmaceutical composition of the present invention may comprise as an active ingredient one or more compounds of the present invention, e.g. at least one, and one or more other pharmaceutically active agents. At least one compound of the present invention thus may be used for pharmaceutical treatment alone, or in combination with one or more further pharmaceutically active agents. Such further pharmaceutically active agents include e.g. retinoids, e.g. retinoic acid, such as isotretinoin; tretinoin (Roche); adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid); oral contraceptives, e.g. 19- nor-17a-pregna-1,3,5(10)-trien-20-in-3,17-diol, 6-Chlor-17-hydroxy-1a,2a-methylen-4,6- pregnadien-3,20- dion, such as Diane® (Schering), antibacterials, such as erythromycins, including

erythromycin A, azithromycin, clarithromycin, roxythromycin; tetracyclines, lincosamid-antibiotics, such as clindamycin (methyl 7-chlor-6,7,8-tridesoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidin-carboxamido)-1-thio-L-threo-a-D-galacto-octopyranosid), azelaic acid (nonanedionic acid), nadifloxacin; dapsone, benzoyl peroxide; keratolytics, such as salicylic acid; anti-inflammatory agents, such as corticosteroids, pimecrolimus; steroid 5α-reductase inhibitors.

For the treatment of breast and endometrial cancer further pharmaceutically active agents include aromatase inhibitors, such as anastrozole, letrozole, exemestane.

Combinations include

- fixed combinations, in which two or more pharmaceutically active agents are in the same pharmaceutical composition,
- kits, in which two or more pharmaceutically active agents in separate compositions are sold in the same package, e.g. with instruction for co-administration; and
- free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

In another aspect the present invention provides a compound of the present invention in combination with at least one other pharmaceutically effective agent for use as a pharmaceutical, such as a pharmaceutical composition comprising a combination of at least one compound of the present invention with at least one other pharmaceutically effective agent in association with at least one pharmaceutical acceptable excipient.

In the following example which illustrate the invention references to temperature are in degrees Celsius.

The following abbreviations are used:

m.p.: melting point

EtAc: ethyl acetate

BOC: tert.butyloxycarbonyl

DMF: N,N-dimethylformamide

RT: room temperature

DMSO: dimethylsulfoxide

Example 1

***N*-[[4-[1-(2-Amido-4-trifluoromethyl-phenyl)]-piperidinyl]-amino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide**

A) 4-[*N*-(Aminosulfonyl)-benzylamino]-piperidine-1-carboxylic acid tert.butylester

A solution of 2.05 g of 4-benzylamino-piperidine-1-carboxylic acid tert.-butyl ester and 3.39 g of sulfamide in 100 ml of 1,2-dimethoxy-ethane is refluxed for ca. 10 hours. From the mixture obtained solvent is evaporated, the evaporation residue obtained is treated with EtAc and unsoluble parts are filtrated off. The filtrate obtained is subjected to chromatography on silica gel. 4-[*N*-(Aminosulfonyl)-benzylamino]-piperidine-1-carboxylic acid tert.butylester is obtained. mp 140-142°. ^{1}H-NMR (DMSO) δ: 7.30-7.41 (s/m, 9+2H), 1.64 (m, 2H), 2.53-2.72 (broad, 2H), 3.71 (tt, 1H), 8.83-8.96 (broad, 2H), 4.26 (s, 2H, CH2), 6.86 (bs, 2H, NH), 7.19 (t, 1H), 7.28 (t, 1H), 7.36 (d, 1H). ^{13}C-NMR (DMSO) δ: 28.51, 30.13, 43.35, 47.11, 56.52, 79.12, 127.06, 127.48, 128.49, 140.59, 154.156.

B) *N*-(1-BOC-4-Piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide

280 mg of diisopropyl-ethylamine and 1.28 ml of n-propylphosphonic anhydride (50% solution in DMF) are added to a solution of 400 mg of 4-[*N*-(Aminosulfonyl)-benzylamino]-piperidine-1-carboxylic acid tert.butylester and 560 mg of 3,5-bis-(trifluoromethyl)benzoic acid in 15 ml of DMF. The mixture obtained is stirred for ca. 4 days at RT, solvent is evaporated and the evaporation residue is treated with EtAc and washed with 1 N HCl, sat. $NaHCO_3$ solution and brine and dried.From the dried residue solvent is evaporated and the evaporation residue obtained is subjected to chromatograpy on silica gel. *N*-(1-BOC-4-Piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide is obtained. ^{1}H-NMR (DMSO) δ: 1.28-1.40 (m, 9+2H), 1.60 (m, 2H), 2.54-2.70 (m, 2H), 3.80-3.94 (m, 2+1H), 4.55 (s, 2H,CH2), 7.18 (t, 1H), 7.27 (d, 1H), 7.37 (d, 1H), 8.26 (s, 1H), 8.46 (s, 2H), 12.6 (broad, 1H, NH).

C) *N*-(4-Piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide in the form of a hydrochloride

A solution of 650 mg of *N*-(1-BOC-4-piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide in 5 ml of CH_2Cl_2 is treated with 60 ml of 3 N HCl (gas) in diethylether. The mixture obtained is stirred for ca. 12 hours and solvent is evaporated. *N*-(4-Piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide in the form of a hydrochloride is obtained.^{1}H-NMR (DMSO) δ: 1.72-1.86 (m, 4H), 2.90 (m, 2H), 3.20-3.3 (m, 2H), 4.15 (m, 1H), 4.60 (s, 2H, CH2), 7.31 (t, 1H), 7.40 (t, 1H), 7.48 (d, 1H), 8.38 (s, 1H), 8.48 (s, 2H), 8.48 and 8.75 (broad, 2H, NH).

D) *N*-[[4-[1-(2-Amido-4-trifluoromethyl-phenyl)]-piperidinyl]-benzylamino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide

430 mg of 2-fluoro-4-trifluoromethyl-benzamide and 430 mg of K_2CO_3 are added to a solution of 570 mg of *N*-(4-piperidinyl-benzylamino)-sulfonyl-3,5-bis-trifluoromethyl-benzamide hydrochloride in 15 ml of DMSO. The mixture obtained is stirred for ca. 4 hours at 150° and K_2CO_3 is removed by filtration. Solvent from the filtrate obtained is evaporated and the evaporation residue is subjected to chromatography on silica gel. *N*-[[4-[1-(2-Amido-4-trifluoromethyl-phenyl)]-piperidinyl]-benzylamino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide is obtained. ^{1}H-NMR (DMSO) δ: 1.60-1.76 (m, 4H), 2.72 (m, 2H), 3.13 (m, 2H), 3.78 (m, 1H), 4.55 (s, 2H, CH2), 7.14 (t, 1H), 7.23 (t, 1H), 7.26 (d, 1H), 7.32 (d, 1H), 7.41 (d, 1H), 7.59 (broad, 1H, NH), 7.68 (d, 1H), 8.08 (broad, 1H, NH), 8.12 (s, 1H), 8.45 (s, 2H).

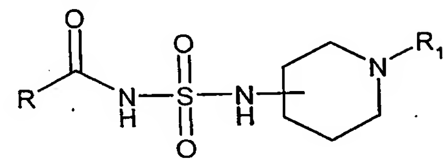
E) *N*-[[4-[1-(2-Amido-4-trifluoromethyl-phenyl)]-piperidinyl]-amino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide

830 mg of *N*-[[4-[1-(2-amido-4-trifluoromethyl-phenyl)]-piperidinyl]-benzylamino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide are dissolved in 20 ml of MeOH and the mixture obtained is hydrogenated for ca. 12 hours at 40° in the presence of 10 % palladium on charcoal. The catalyst is filtered off and the filtrate obtained is subjected to chromatography chromatographed on silica gel. *N*-[[4-[1-(2-Amido-4-trifluoromethyl-phenyl)]-piperidinyl]-amino]-sulfonyl-3,5-bis-trifluoromethyl-benzamide is obtained. mp 192-195 °C.
^{1}H-NMR (DMSO) δ: 1.58 (m, 2 H), 1.94 (m, 2 H), 2.77 (m, 2 H), 3.11-3.21 (m, 3 H), 5.8 (broad, 1 H, NH), 7.32 (s, 1 H), 7.36 (d, 1 H), 7.69 (broad, 1 H), 7.74 (d, 1 H), 8.16 (s,1 H), 8.22 (broad, 1 H), 8.48 (s, 2 H).

Patent claims

1. A phenylcarbonyl-sulfamic acid N-piperidinyl-amide.

2. A comüpound according to claim 1 of formula



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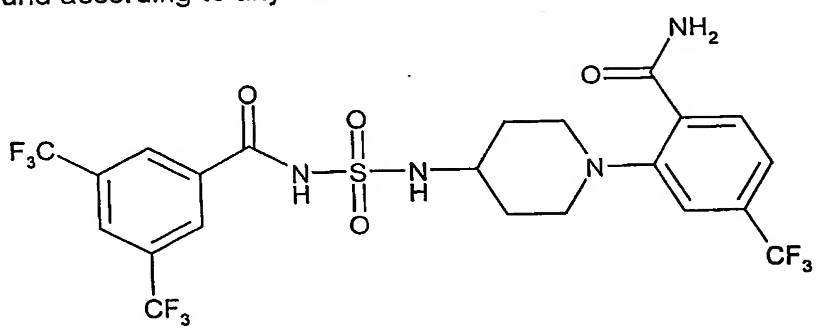
wherein
R is unsubstituted or substituted phenyl, and
R_1 is alkoxycarbonyl, or unsubstituted or substituted phenyl.

3. A comüpound according to any one of claims 1 or 2 of formula



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4. A compound of any one of claims 1 to 3 in the form of a salt.

5. The use of a phenylcarbonyl-sulfamic acid N-piperidinyl-amide in the preparation of a medicament for the treatment of a disorder mediated by the action of steroid sulfatase, such as acne.

6. A method of treating disorders mediated by the action of steroid sulfatase comprising administering a therapeutically effective amount of a phenylcarbonyl-sulfamic acid N-piperidinyl-amide to a subject in need of such treatment.

7. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of any one of claims 1 to 4 in association with at least one pharmaceutically acceptable excipient.

8. A compound of any one of claims 1 to 4 for use as a pharmaceutical.

9. A compound of any one of claims 1 to 4 in combination with at least one other pharmaceutically effective agent for use as a pharmaceutical, such as a pharmaceutical composition comprising a combination of at least one compound of the present invention with at least one other pharmaceutically effective agent in association with at least one pharmaceutical acceptable excipient.

Abstract

A phenylcarbonyl-sulfamic acid N-piperidinyl-amide, useful as a pharmaceutical.